CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022416Orig1s000

OTHER ACTION LETTER(s)

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022416 **COMPLETE RESPONSE**

Sepracor Inc.
Attention: Karen Joyce
Associate Director Regulatory Affairs
84 Waterford Drive
Marlborough, MA 01752

Dear Ms. Joyce:

Please refer to your March 29, 2009 New Drug Application (NDA), received March 30, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Stedesa, (eslicarbazepine acetate) 400 mg, 600 mg, and 800 mg Tablets.

We acknowledge receipt of your amendments dated:

April 15, 2009	September 25, 2009	November 24, 2009	February 10, 2010
April 22, 2009	September 29, 2009	December 24, 2009	February 12, 2010
May 12, 2009	October 2, 2009	December 10, 2009	March 4, 2010
June 18, 2009	October 7, 2009	January 8, 2010	
July 9, 2009	October 14, 2009	January 13, 2010	
July 13, 2009	October 20, 2009	January 25, 2010	
July 31, 2009	October 30, 2009	January 29, 2010	
August 28, 2009	November 13, 2009	February 4, 2010	

We also acknowledge receipt of your amendments dated March 10, 2010 and April 13, 2010, which were not reviewed for this action. You may incorporate applicable sections of these amendments by specific reference as part of your response to the deficiencies cited in this letter.

We have completed our review of your application, as amended, and have determined that we cannot approve this application in its present form. We have described below our reasons for this action and, where possible, our recommendations to address these issues.

Significant and serious deficiencies in your application and/or data make it impossible for us to reach any definitive conclusions about the safety and effectiveness of eslicarbazepine acetate.

The clinical deficiencies fall into two general categories: 1) deficiencies in the conduct and documentation of your studies, based on inspections of several study sites, and 2) deficiencies in the structure of your application, including deficiencies in the accuracy, reliability, and presentation of the data. We will discuss these in turn.

Deficiencies Related to the Conduct and Documentation of the Studies

A total of four clinical investigator sites, and your firm as the applicant, were audited to evaluate the conduct of the following clinical trials supporting the requested indication:

- Protocol BIA-2093-301, entitled "Efficacy and safety of BIA 2-093 as adjunctive therapy for refractory partial seizures in a double-blind, randomized, placebo-controlled, parallel-group, multicenter clinical study"
- Protocol BIA-2093-302, entitled "Efficacy and safety of BIA 2-093 as adjunctive therapy for refractory partial seizures in a double-blind, randomized, placebo-controlled, parallel-group, multicenter clinical trial"

A third phase 3 study, Protocol BIA-2093-303, was conducted in support of the drug development program; however, prior to NDA submission, you determined that this study should not be used to support efficacy because of significant good clinical practice (GCP) violations identified during audits of clinical investigator sites that participated in the study.

Clinical Investigator Inspections

A total of four foreign clinical investigator inspections by FDA, two each for Studies BIA-2093-301 and BIA-2093-302, have been completed as part of the data audit for this NDA. For Study BIA-2093-301, data from one of two clinical investigators (Dr. Danilo Hodoba) audited by FDA are not considered reliable in support of this NDA. For Study BIA-2093-302, data from one of two clinical investigators (Dr. Carmen Diaz-Obregon) audited by FDA are not considered reliable in support of this NDA.

The data from the two sites listed above fall into the following categories:

- Failure to conduct the study(ies) according to the signed investigator statement and the investigational plan [21 CFR 312.60].
- Failure to prepare and maintain adequate and accurate case histories with respect to observations and data pertinent to the investigation [21 CFR 312.62(b)].
- Failure to document and report adverse events to the sponsor [21 CFR 312.64].
- Failure to prepare and maintain adequate drug accountability records of disposition of the drug, including dates, quantity, use by subjects, and amount returned by each subject [21 CFR 312.62(a)].

Below we describe several examples of the significant deficiencies noted at these sites. The examples given do not constitute a complete list of the deficiencies discovered by our inspections.

Study 301, Dr. Hodoba

1) There was neither identification of the investigational product kit assigned to the subjects nor lot numbers on the drug accountability log. This made it impossible to verify proper drug dispensation to subjects. In addition, all drug product and related labeling were destroyed prior to the inspection, making verification of returned drug impossible. Furthermore, the drug accountability records were inadequate, in that there was a lack of documentation for the returned test article, and there was a lack of adequate documentation of the amount of investigational drug dispensed.

2) For several subjects the records showed that the number of tablets destroyed was inexplicably greater than the number of tablets returned. For example, Subject 1251 returned 72 tablets, but 94 tablets were reported as having been destroyed. Another patient, Subject 1269, was dispensed drug assigned to Subject 1272.

3) Several patients (e.g., Subjects 1250 and 1249) had English translations of their diaries without documentation of the name of the translator.

4) For Subjects 1250 and 1249 and other patients, seizure counts listed in the diaries for various intervals during the study were not recorded in the data listings.

5) Subject 1264 was discontinued from the study because of a low white cell count, as recorded in the Case Report Form (CRF). However, this was not recorded as such in the data listings in the application.

Study 302, Dr. Diaz-Obregon

1) At least four subjects did not have the protocol-specified number of partial seizures in each 4-week period during the baseline period. According to Dr. Matias-Guiu, waivers were granted for these patients, but these waivers were not approved until after the patients were enrolled in the trial. In addition, there was no documentation of when or how many seizures these patients experienced during the baseline period.

2) Source documentation for seizure counts for several patients was missing. Furthermore, there were discrepancies in the numbers of seizures recorded in the diaries and in the CRFs for some patients.

3) The records at this site were out of sequence and difficult to verify. Medical charts and source documents were neither labeled nor signed, and included handwritten notes and "sticky notes." Some typed progress notes had handwritten entries with no initials for the person making the entries or reason for the notes. The disarray of the records made verification of the study conduct very difficult.

In addition, you determined that multiple investigators participating in Study BIA-2093-303 had been significantly noncompliant with Good Clinical Practice during their participation in Study

BIA-2093-303 and data from this study should not be relied on to support efficacy. Given the nature of GCP issues reported by you, across a majority of sites enrolling subjects in this study, the FDA also has concerns with the use of data from this study to support the safety of eslicarbazepine acetate.

Evaluation of Sponsor and Applicant Audit Reports Submitted to the NDA

At the request of the review division, you submitted reports for audits of clinical investigator sites enrolling subjects in Studies BIA-2093-301, BIA-2093-302, and BIA-2093-303. These audits were conducted by the sponsor of these studies, BIAL, and yourself. Based on our review of these audit reports, we have determined that the audit reports disclosed significant GCP violations and noncompliance with commonly accepted good clinical practices and federal regulations. For example, the audits observed discrepancies between the number and type of adverse events recorded in the source documents and the CRFs for numerous patients in all studies. While we acknowledge that you responded to apparent discrepancies in your submission dated 1/25/10, the remaining time in the review clock did not allow for definitive evaluation of your response. Importantly, such audit reports constituted only a fraction of the total subjects investigated, raising concerns regarding the remaining unaudited sites. Given the limited number of subject records examined at audited sites, we do not find the results of these audits to be sufficient in scope or detail to allow for adequate assessment of data reliability.

These deficiencies, taken together, raise serious questions about the integrity of the data derived from these studies. Although we are asking you to submit responses to the requests below, we are not confident that you can provide all of the information requested, or, if you can, that the responses will adequately address all of our concerns. You should be aware that we are likely to request that you conduct at least one more controlled trial under acceptable and accepted clinical practices.

In order to address the issues outlined above, we request that you:

1. Provide the following information regarding BIAL's QA audit program:
    a. A report of the sponsor's QA audit plan, including the sponsor's plan for securing compliance from non-compliant clinical investigators. Include copies of any Standard Operating Procedures (SOPs) that were in place during conduct of the study to address means by which corrective actions were to be taken for identified noncompliant clinical investigators.
    b. Provide a description for BIAL's QA program with respect to the oversight of the CROs that were hired to monitor the clinical sites. Describe the procedures implemented to ensure that the CROs adequately monitored the clinical sites. In your response, include the following information:
        i. How was Bial kept apprised by the CROs concerning monitoring of the clinical sites during the course of the studies? Specifically, what information was provided by the CROs? Provide a list of non-compliant clinical study sites reported by CROs.

ii. How did Bial review the information from the CROs, during the course of the study(ies) and at the close of the study? What monitoring information was retained at the end of the study(ies)?
iii. What actions, if any, did Bial take based on the information received from the CROs monitoring reports? If no actions were taken, why not?

c. A report of any corrective actions taken and final outcome for sites audited under the sponsor's QA program.
d. A list of all non-compliant sites, including the steps that were taken by the sponsor of the study to ensure compliance and the reporting procedures used to report this noncompliance to the FDA.

2. Please provide assurance that safety and efficacy data obtained in Studies BIA-2093-301 and BIA-2093-302 are reliable. We suggest that you, or preferably a third party, perform additional audits of clinical sites that enrolled subjects in these studies.
   a. Please describe the following information regarding your intended audit plan:
      i. How many clinical sites will be audited, how will clinical sites be selected, and how many subject records will be examined per site for your targeted audit?
      ii. If not all subject records at a given clinical site will be audited, describe how subject records will be sampled and how the specific data from each subject will be audited.
   b. Please describe the timeline for completing your audit.
   c. When available, please provide a report of your audit results. Please also include, at each clinical site audited, the numbers of violations identified for each category, below. For each specific violation, list the clinical sites involved and provide a breakdown by treatment group for each site and overall for the three BIA 2-093 studies (BIA-2093-301, BIA-2093-302, and BIA-2093-303). The following issues should be addressed:

      i. Enrollment of subjects who did not meet study eligibility criteria.
      ii. Sites at which the clinical investigator failed to ensure all associates and colleagues assisting in the investigation were adhering to the study protocol and where the clinical investigator failed to provide oversight over the conduct of the study and staff.
      iii. Failure to report adverse events in a timely manner.
      iv. Failure to obtain informed consent from all subjects prior to performing study procedures.
      v. Failure to maintain adequate drug accountability records. State whether a pharmacist was involved.
      vi. Failure to randomize subjects according to plan (sequential).

      Please list the clinical sites where BIAL or CRO monitoring is determined to be ineffective, either in identifying significant violations or in taking actions toward securing compliance (such as terminating the site and notifying the sponsor and FDA in a timely manner).

Deficiencies Related to the Presentation of the Data in the Application

Throughout our review, we have noted a number of deficiencies and inconsistencies in the information you have submitted in the application. Although some issues were minor in nature, others were important, and served to undercut the review team's confidence in the reliability of the data. Although we have requested that you conduct various audits, we are not certain that you will be able to adequately salvage the study data to reassure us as to its veracity. It is possible that additional studies may be required.

In addition, given the scope of problems you identified in Mexican study sites in study BIA-2093-303, we do not regard the study as supportive, even from the standpoint of safety. Safety analyses are fundamentally non-inferiority analyses, and random noise, as might be generated from poor study execution, would tend to obscure differences and provide false reassurance.

In addition to the above two general categories of deficiencies, we have the following specific comments:

ABUSE LIABILITY

We also note your February 10, 2010 response to comments from the Controlled Substances Staff (CSS), sent to you on January 4, 2010 and January 13, 2010. Although we do not agree with your interpretation of the animal abuse studies, our primary concerns are related to the reliability of the clinical data relevant to these issues. For many of the same reasons described above, we consider the human data relevant to an assessment of abuse liability and dependence unreliable. Therefore, we ask you to provide the following additional information:

- Conduct an appropriate and well-designed human abuse potential study with eslicarbazepine acetate. CSS is available to evaluate the protocol design and provide feedback prior to the start of the study.
- Conduct a two-week prospective evaluation of physical dependence – typically this would be conducted at the conclusion of the clinical efficacy study. CSS is available to evaluate the protocol design and provide feedback prior to the start of this study.
- Update the reporting of adverse events in clinical studies to the most recent version of MedDRA used in the NDA (i.e., MedDRA 10.0) by using the verbatim descriptions that occurred during clinical trials.
- Provide an analysis of all abuse-related AEs, using the terms provided previously by CSS.

STATISTICAL

The studies only required the participants to update their seizure diaries when they experienced a seizure. As a result, failure to record seizures (i.e., missing data) could not be differentiated from

the absence of seizure. Therefore, a worst-case imputation of all missing data (not just missing diary cards) is not possible. This limited our evaluation of the robustness of the efficacy results.

Moreover, we note that the extensive use of hardcodes, performed to correct data errors (based on blinded and unblinded reviews of data), further supports our concern regarding the marginal quality of data provided in this study.

The extensive problems described in the conduct of the studies as well as in the reporting of the data raise significant questions about the reliability of the data. The deficiencies in the presentation of the data in your application further complicated our ability to rely on, and have hampered our ability to independently review, the data.

We will be happy to discuss with you in more detail the specifics of the deficiencies, and potential approaches to resolving them. However, as we noted above, it is possible that such a restructuring and resubmission may not be adequate to address all of our concerns.

CLINICAL PHARMACOLOGY

You should consider developing a lower strength (200 mg) of Stedesa to allow everyday dosing during the titration phase in patients with severe renal impairment. Lower strengths are also appropriate for use in the elderly population.

NONCLINICAL

You have not fully addressed our previous request (Agency letter dated January 26, 2007) for documentation of the adequacy of the *in vitro* assays for assessing the genotoxic potential of eslicarbazepine, the major circulating metabolite in humans. You have conducted an *in vitro* Ames assay testing eslicarbazepine directly and an *in vivo* micronucleus assay in the mouse (a species in which eslicarbazepine is a major circulating metabolite). However, you have not demonstrated that eslicarbazepine acetate was adequately tested in the *in vitro* chromosomal aberration assays in mammalian cells or the *in vitro* mouse lymphoma tk assay since, in these assays, the metabolic activation system (liver S9) was from rat. The metabolic profile in rat is sufficiently different from human that the need for carcinogenicity assessment in this species was waived.

Due to the increase in hepatic tumors observed in the 2-year mouse carcinogenicity study, and considering the lack of an assessment of carcinogenic potential in a second species, a full characterization of the genotoxic potential of eslicarbazepine is important. We ask that you address this, either by demonstrating that the completed assays are adequate, or by conducting either an *in vitro* chromosomal aberration assay in mammalian cells or an *in vitro* mouse lymphoma tk assay (with colony sizing), testing eslicarbazepine directly with and without an appropriate metabolic activation system.

LABELING

1. We reserve comment on the proposed labeling until the application is otherwise adequate. If you revise labeling, your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm.

   We note your response submitted on April 13, 2010 to the Division's Clinical Pharmacology and Chemistry, Manufacturing, and Controls labeling edits sent to you on March 31, 2010.

2. Please submit draft carton and container labeling revised as follows:

   A. General Comments (All Labels and Labeling)

      1. We note the proprietary name is presented in all-caps. Consider revising the proprietary name to appear in title case (i.e., Stedesa). Words set in upper and lower case form recognizable shapes, making them easier to read than the rectangular shape that is formed by words set in all-caps. In addition, consider revising the established name so that "eslicarbazepine acetate" appears in parentheses and consider revising the presentation of the dosage form to appear in title case (i.e., Tablets).

      2. Add the following bolded statement or appropriate alternative to the carton and container labels per 21 CFR 208.24(d): "**ATTENTION PHARMACIST: Each patient is required to receive the enclosed Medication Guide.**"

   B. Container Labels: 30 count bottle (400 mg and 800 mg)

      1. De-bold the net quantity statement so it appears less prominent then the product strength to avoid confusion and misinterpretation of these numbers.

      2. Revise the statement, [redacted] (b) (4) to read "Usual Dosage: See package insert for dosage information."

   C. Container Labels: 60 count bottle (600 mg)

      1. See Comments B.1. - B.2. above.

   D. Container Labels: 90 count bottle (600 mg and 800 mg)

      1. See Comments B.1. - B.2. above.

      2. We note that although the 90 count bottle may be a unit-of-use container, it may also be used for more than one patient. Ensure a sufficient number of medication guides are provided.

   E. Professional Samples (Carton labeling):
   7 count (400 mg); 10 count (600 mg, 800 mg)

      1. See Comment B.2. above.

2. To ensure the entire contents of the carton is not misinterpreted as one single dose, revise the presentation of the strength through either of the following statements, "XX mg per tablet," "XX mg/tablet," or "Each tablet contains 100 mg."

F. Professional Samples (Blister Card):
7 count (400 mg); 10 count (600 mg, 800 mg)

Ensure that the established name is at least one-half the size of the proprietary name and the established name shall have a prominence commensurate with the prominence with which such proprietary name appears, taking into account all pertinent factors, including typography, layout, contrast, and other printing features per 21 CFR 201.10(g)(2). Revise accordingly.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(*b*). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:
   - Present new safety data from the studies/clinical trials for the proposed indication using the same format as the original NDA submission.
   - Present tabulations of the new safety data combined with the original NDA data.
   - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
   - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

6. Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).

7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

8. Provide English translations of current approved foreign labeling not previously submitted.

PROPOSED PEDIATRIC STUDY REQUEST

We note that, on August 29, 2009, you submitted to this application a Proposed Pediatric Study Request (PPSR) as your Pediatric Plan required under the Pediatric Research and Equity Act. We reserve comment on your PPSR until the application is otherwise adequate. However, we ask that you resubmit your PPSR as part of your response to this letter.

RISK EVALUATION AND MITIGATION STRATEGY (REMS) REQUIREMENTS

As described in our letter dated November 4, 2009, in accordance with section 505-1 of the FDCA, we have determined that a risk evaluation and mitigation strategy (REMS) is necessary for Stedesa (eslicarbazepine acetate) to ensure that the benefits of the drug outweigh the increased risk of suicidal thoughts and behavior.

We acknowledge receipt of your proposed REMS submitted on December 4, 2009, and amended on January 8, 2010, consisting of a Medication Guide and a timetable for submission of assessments of the REMS. We will continue discussion of your proposed REMS after your complete response to this action letter has been submitted. Our review of any additional data that you submit in response to this letter may necessitate changes to your proposed REMS.

OTHER

Within one year after the date of this letter, you are required to resubmit or take one of the other actions available under 21 CFR 314.110. If you do not take one of these actions, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA's *Guidance for Industry - Formal Meetings Between the FDA and Sponsors or Applicants*, May 2009 at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, call Dorothy Demczar, Pharm.D., Regulatory Project Manager at (301) 796-2263.

Sincerely,

{See appended electronic signature page}

Ellis F. Unger, M.D.
Deputy Director
Office of Drug Evaluation I
Center of Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22416	ORIG-1	SEPRACOR INC	SEP-0002093 ESLICARBAZEPINE ACETATE
NDA-22416	GI-1	SEPRACOR INC	SEP-0002093 ESLICARBAZEPINE ACETATE

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/s/

ELLIS F UNGER
04/30/2010